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54, as this claim is a member of the elected group (Group V). Regardless, the Examiner retained and examined Claim 54 in the present Office Action. For clarification, it is the Applicant's intention that Claim 54 be examined and passed to allowance. Applicants also note a clerical error in the Office Action on page 2, paragraph 2. In the first line of that paragraph, Group V should include Claims 42-54 and 73-76, and not 42-54 and 75-76 as written.

All amendments to the Specification are to correct typographical and clerical errors. Support for the amendment on page 2, line 16, is found on page 22, lines 12-13, where the information is shown correctly. Support for the amendment on page 23, lines 13-14 can be found at various places in the Specification, especially page 29, lines 6-17, TABLE 1 at page 31 (SEQ ID NOs: 27 and 28), and SEQ ID NOs: 176 and 177. The substitute TABLE 1 is supplied for the purpose of correcting typographical errors in the table and to fix column and row formatting. Other amendments to the Claims are discussed below.

Applicants also enclose an amended substitute paper copy of the "Sequence Listing," as well as a substitute copy of the computer readable form of the "Sequence Listing" to be made of record in this case in accordance with 37 C.F.R. § 1.825. This substitute sequence listing is to correct the species designation of SEQ ID NOs: 176 and 177. These sequences are peanut (*Arachis hypogaea*) allergen sequences termed Ara h2 allergens, and not *Homo sapiens* allergens, as was inadvertently indicated. Support for this change can be found on page 29, lines 14-17, where these allergen sequences are correctly identified as peanut allergens.

None of the amendments to the Specification, Claims or Sequence Listing constitute new matter.

Rejections under 35 U.S.C. 112, first paragraph

(A) *Enablement*

In the Office Action dated October 10, 2001, the Examiner rejects Claims 1-6, 22-27, 29-30, 40-52, 54 and 73-76 for allegedly lacking enablement (35 U.S.C. § 112, first paragraph), for various reasons (see Office Action, pages 2-6). The Examiner alleges that the specification does not provide enablement commensurate in scope with the claims without undue experimentation. Specifically, the Examiner alleges that the following fusion molecules are not enabled by the disclosure of the Specification:

- 1) fusion molecules "comprising" first and second polypeptide sequences,

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- 2) fusion molecules comprising a first polypeptide having at least 90% sequence identity with the amino acid sequence of SEQ ID NO: 3 (*i.e.*, the IgG<sub>1</sub> heavy chain hinge-CH<sub>2</sub>-CH<sub>3</sub> constant domain) or 90% sequence identity with a heavy chain constant domain of IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub> or IgG<sub>4</sub>,
- 3) fusion molecules comprising a second polypeptide having at least 90% sequence identity with the amino acid sequence of SEQ ID NO: 6,
- 4) fusion molecules comprising a first polypeptide encoded by a nucleic acid hybridizing under stringent conditions to the nucleotide sequence of SEQ ID NO: 1, which encodes the IgG<sub>1</sub> heavy chain constant domain, and
- 5) fusion molecules comprising a second polypeptide encoded by a nucleic acid hybridizing under stringent conditions to the nucleotide sequence of SEQ ID NO: 4, which encodes the IgE heavy chain constant domain.

Also in the Office Action, the Examiner admits that certain fusion molecules of the present invention are enabled, namely:

- 1) the fusion molecule of SEQ ID NO: 7, which consists of the IgG heavy chain constant domain as provided in SEQ ID NO: 3 and the IgE heavy chain constant domain as provided in SEQ ID NO: 6,
- 2) the fusion molecules where the first polypeptide is at least a portion of the IgG heavy chain constant domain as provided in SEQ ID NO: 3 connected to at least a portion of the IgE heavy chain constant domain,
- 3) the fusion molecules above, where the two polypeptides are fused to each other or are connected by a polypeptide linker, and
- 4) the fusion molecules above, where the molecules form homodimers through disulfide bonds.

Applicants must respectfully disagree with the Examiner's rejection of the claims.

#### *Legal standard*

The test for enablement entails an analysis of whether one skilled in the art is able to practice the invention using information disclosed in the application and information known in the art without undue or unreasonable experimentation (MPEP § 2164.01; see *In re Wands*, 858

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F.2d 731, 8 USPQ2d 1400, [Fed. Cir. 1988]). A finding of lack of enablement and determination that undue experimentation is necessary requires an analysis of a variety of factors (*i.e.*, the *In re Wands* factors). The most important factors that must be considered in this case include 1) the nature of the invention; 2) the level of ordinary skill in the art; 3) guidance provided in the specification; and 4) the state of the prior art. “[H]ow a teaching is set forth, by specific example or broad terminology, is not important”; and furthermore still, “[L]imitations and examples in the specification do not generally limit what is covered by the claims” (MPEP § 2164.08). The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; 169 USPQ 759, 762-63 (2d Cir. 1971), cert. denied, 404 U.S. 1018, 30 L. Ed. 2d 666, 92 S. Ct. 680 (1972). The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed. *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 1362 (Fed. Circ. 1999), at 1372 (quoting *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991).

Proper application of the legal standard must lead to the conclusion that all claims pending in this application are fully enabled. Since the first two *In re Wands* factors listed above are relevant to all rejections, it seems appropriate to start with their analysis, before turning to the claim-specific issues.

#### *The nature of the invention*

The present invention is from the field of recombinant DNA technology and immunology. In particular, the invention concerns certain novel fusion molecules that are capable of cross-linking a native IgG inhibitory receptor comprising an ITIM motif with a native IgE receptor, and find utility in the management of IgE-mediated allergic diseases and other disorders mediated by IgE receptors. While the therapeutic strategy underlying the present

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invention is both novel and unobvious, the fusion molecules themselves have a relatively simple structure, and can be made and tested by standard techniques that were well known in the art at the time of making the present invention. Furthermore, at the time the present invention was made, there was a lot of information known in the art about the interaction of IgG inhibitory receptors and IgE receptors with antibody constant regions, which provides valuable information for the construction of the fusion molecules of the present invention. Accordingly, although unpredictability in the field of recombinant DNA technology is generally viewed as relatively high, the unpredictability in the particular field to which the present invention pertains is of lesser degree.

*The level of ordinary skill in the art*

It is well established that the level of skill in the art of recombinant DNA technology is relatively high, and is typically represented by the knowledge of a Ph.D. scientist with several years of experience in the pertinent field.

*Fusion Molecules Comprising First and Second Polypeptide Sequences are Enabled*

The Examiner reasons that fusion molecules “comprising” first and second polypeptide sequences are not enabled, as use of the term “comprising” leaves the sequence of the IgG constant domain unpredictable, and further, makes other amino acid sequences in the fusion molecule in addition to the IgG and IgE constant domain sequences unpredictable, and thus, makes the function of the fusion molecule unpredictable (Office Action, page 5, paragraph starting on line 3).

Applicants must respectfully disagree. The present application describes, by way of example, additional non-essential but advantageous amino acid sequences and other elements that find use with the first and second polypeptides of the fusion molecules of the invention. For example, the first and second polypeptide sequences of the fusion molecule can be joined using various linkers (described in the Specification at page 27, lines 4-15). Also, the fusion molecules may contain posttranslational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation and prenylation (see Specification page 12, line 24, through page 13, line 13). The Specification teaches that fusion polypeptide variants can be constructed that contain advantageous insertions of various amino acid sequences (page 14, lines 11-14), resulting

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in fusion molecules that have improved affinity for their respective IgG or IgE Fc receptors (Specification, page 21, lines 9-28). The fusion molecules of the invention can also comprise multiple copies of the IgG and IgE Fc domains, for example, IgG-IgG-IgE or IgG-IgE-IgG Fc configurations find use with the invention, as described in page 25, lines 6-17. Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 42, lines 17-19), and peptide sequence tags to facilitate fusion molecule purification (page 42, lines 29-31) also find use with the fusion molecules of the invention.

As outlined above, the Specification provides sufficient guidance to make a variety of advantageous fusion molecules comprising first and second polypeptide sequences. Applicants submit that fusion molecules comprising first and second polypeptides are fully enabled in view of 1) guidance provided throughout the Specification<sup>1</sup> (as described above), 2) the routine nature of recombinant DNA engineering and the production of chimeric or variant polypeptides, as known in the art, and 3) the high level of technical competence of one of ordinary skill in the immunological, genetics and protein-chemistry arts. The routine nature of manipulation of DNA and protein molecules is well known, as evidenced by the publications cited in the Specification (*see*, especially, page 12, line 20 through page 13, line 13, page 28, lines 19-27, page 41, lines 1-25, and page 43, line 24 through page 44, line 21). Detailed protocols for the construction of the fusion molecule variants described in the Specification is not necessary for one of ordinary skill to practice the claimed invention without undue experimentation.

The Examiner asserts that use of the term “comprising” in the claims results in an infinite number of possible nucleotide sequences, and it is not possible to predict which of those molecules will have desired functional activity. Applicants disagree. Applicants point out that Claim 1 and all claims dependent on Claim 1 contain the functional limitation that the IgG and IgE Fc domains (either native or variants) have the ability to bind to their respective cell surface receptors, and the Specification teaches which amino acids are necessary for receptor binding (*see* page 21, lines 9-28) as well as methods to determine the affinity of an Fc domain for its cognate receptor (*see*, for example, page 26, lines 15-25). Thus, use of the term “comprising” does not result in an infinite number of fusion molecules with unpredictable activities, and the identification of constructs that meet the limitation of the claims does not require undue experimentation.

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Applicants submit that use of the open-ended transitional phrase “comprising” in Claims 1, 29, 40-45 and 47 is appropriate, and those claims as well as all claims dependent on those claims are enabled and commensurate in scope with the disclosure, and are allowable. The Examiner is respectfully requested to withdraw this rejection.

*Fusion Molecules Comprising First and/or Second Polypeptide Sequences Having “90% Sequence Identity” with an Ig Heavy Chain Constant Region are Enabled*

The Examiner alleges that the disclosure of the Specification provides insufficient guidance to make and use polypeptides having at least 90% sequence identity with the IgG and IgE constant domain sequences of SEQ ID NOs: 3 and 6, respectively, where the molecules retain biological or immunological function (e.g., retaining the ability to inhibit IgE mediated release of histamine). The Examiner also states there are insufficient working examples of polypeptides having 90% sequence identity with known IgG or IgE constant domain sequences that will inhibit IgE-mediated histamine release (Office Action, page 54, paragraph starting on line 12).

Applicants respectfully traverse the rejection. Applicants point out that the Specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 14, line 25 through page 15, line 3)<sup>2</sup>. Also, one of ordinary skill in the art will recognize that the prior art provides numerous sources that describe Ig Fc sequences highly homologous to the Fc sequences of SEQ ID NOs: 3 and 6 (see, the Specification at page 17, line 21 through page 18, line 3). Furthermore, Applicants assert that one of ordinary skill in the art has a sufficiently high level of technical competence to experimentally identify novel Fc sequences having at least 90% sequence identity with the constant domain sequences of SEQ ID NOs: 3 and 6 using hybridization methods provided in the Specification (see, page 15, lines 4-30). Alternatively, one of skill in the art can readily engineer novel Fc domains having at least 90% sequence identity with the constant domain sequences of SEQ ID NOs: 3 and 6 using recombinant DNA/protein engineering techniques. Thus, detailed protocols for the construction of fusion molecules having at least 90% sequence identity with a known Ig constant domain in

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<sup>1</sup> Applicants point out that the guidance provided in the Specification is found both in the Experimental Example as well as in the description of other preferred embodiments elsewhere in the Specification.

<sup>2</sup> Furthermore, the Examiner admits that the application discloses this method for the determination of percent sequence identity (see, Office Action, page 4, bottom paragraph).

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the Specification is not necessary in order for one of ordinary skill to practice the claimed invention without undue experimentation.

Applicants point out that all pending claims reciting polypeptides having at least 90% sequence identity with IgG or IgE Fc domains (*e.g.*, having 90% sequence identity with SEQ ID NOs: 3 or 6) contain the functional limitation that the polypeptides also have the ability to bind to their respective cell surface receptors, and the Specification teaches which amino acids are necessary for receptor binding (see page 21, lines 9-28) as well as methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 26, lines 15-25). Conservation of these critical amino acids results in polypeptides that retain the desired biological activity (receptor binding and inhibition of histamine release). Thus, contrary to the Examiner's statement, use of the phrase "having at least 90% sequence identity" does not result in fusion molecules with unpredictable activities. A person skilled in the art, relying on the teaching of the specification and general knowledge in the art at the time the present invention was made, will be able to determine which amino acid alterations are expected to yield constructs that satisfy the functional limitations of the claims, without undue experimentation.

Applicants submit that in view of disclosure found in the Specification (including, but not limited to the working examples), the state of the prior art, and the high level of skill in the art, use of the phrase "at least 90% sequence identity" in Claims 29, 42 and 54 is appropriate, and those claims as well as all claims dependent on those claims are enabled, commensurate in scope with the disclosure and allowable. The Examiner is respectfully requested to withdraw this rejection.

*Fusion Molecules Encoded by Nucleic Acid "Hybridizing Under Stringent Conditions" to SEQ ID NOs: 1 and/or 4 are Enabled*

The Examiner alleges that Claims 40 and 41 are not enabled, as a "sequence encoded by nucleic acid 'hybridizing under stringent conditions' . . . encompasses any random sequence of any length which hybridizes under nonspecific conditions to the complement of . . . SEQ ID NO: 1 and . . . SEQ ID NO: 4" (Office Action, page 6, paragraph starting on line 8). The Examiner admits that the Specification defines "stringent" hybridization conditions (Office Action, page 4, bottom paragraph).

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Applicants disagree with the Examiner's rejection. As commonly used in the art, and as used in Claims 40 and 41, the phrase "stringent" hybridization conditions implies "high stringency" conditions. These terms are defined and exemplary conditions are provided in the Specification (see page 15, lines 4-30). Contrary to the Examiner's statements, use of high stringency conditions does not result in "random sequence of any length which hybridizes under nonspecific conditions" to SEQ ID NOs: 1 or 4. High stringency conditions are used to identify nonrandom sequences showing strong homology (*i.e.*, relatedness) to the hybridization probe. Furthermore, as required by Claims 40 and 41, polypeptides encoded by nucleic acids that hybridize with SEQ ID NOs: 1 or 4 under stringent conditions must also be capable of specific binding to a native IgG or IgE receptor (see independent Claim 1). Thus, contrary to the Examiner's assertion, "random sequences of any length" are unlikely to meet this limitation. Furthermore, in view of the ability of one of ordinary skill in the art to conduct hybridization screenings using the stringent conditions disclosed, undue experimentation would not be required to practice the claimed invention.

Applicants assert that in view of disclosure found in the Specification, use of "stringent conditions" in Claims 40 and 41 is appropriate, and those claims are enabled and allowable. However, solely for the purpose of better defining the invention, furthering the Applicants' business interests and advancing the prosecution of the present application, and while reserving the right to prosecute the original or similar claims in the future without loss of equivalents, Applicants have amended Claims 40 and 41 to recite exemplary stringent hybridization conditions. Support for this amendment is found in the Specification at page 15, lines 25-30. Applicants respectfully request the withdrawal of this rejection.

(2) *Written Description*

In the Office Action, the Examiner rejects Claims 1-6, 22-27, 29-30, 40-52, 54 and 73-76 for allegedly lacking written description (35 U.S.C. § 112, first paragraph). Specifically, the Examiner alleges that there is insufficient written description in the Specification for the same fusion molecules that were rejected on the basis of lack of enablement (see above, and Office Action, pages 7-8).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the



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inventor had possession of the claimed invention (e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 and *Gentry Gallery, Inc. v. Berkline Corp.*, 134 F.3d 1473, 45 USPQ2d 1498 [Fed. Cir. 1998]). Applicants assert that they have met this requirement. Applicants emphasize that sufficient written description must be ascertained in view of one skilled in the art. "It is not required that the application describe the claim limitations in greater detail than the invention warrants. The description must be sufficiently clear that persons of skill in the art will recognize that the applicant made the invention having those limitations" (*Martin v. Mayer*, 823 F.2d 500, 3 USPQ2d 1333 [Fed. Cir. 1987]).

#### *Multiple Fusion Molecules are Described in the Specification*

The Examiner alleges that the Specification discloses insufficient written description of the structure of fusion molecules of the invention (with the exception of the fusion molecule recited in Claim 53, i.e., SEQ ID NO: 7) to support a claim to a larger genus of fusion molecules.

Applicants must respectfully disagree. As described above, the Specification describes multiple fusion molecules in addition to the fusion molecule of SEQ ID NO: 7. For example, the Specification describes fusion molecules where the first and second polypeptide sequences of the fusion molecule are connected by use of linkers (see Specification page 27, lines 4-15). Also, the fusion molecules may contain post translational modifications, either naturally occurring or artificial, for example, acetylation, glycosylation or prenylation (as described in the Specification at page 12, line 24, through page 13, line 13). The Specification describes advantageous fusion molecule variants (page 14, lines 11-14), where the variants have improved affinity for their respective IgG or IgE receptors (Specification, page 21, lines 9-28). The Specification describes fusion molecules comprising multiple copies of IgG and IgE Fc domains, for example, IgG-IgG-IgE or IgG-IgE-IgG Fc configurations (page 25, lines 6-17). Fusion polypeptides further comprising signal sequences for intracellular localization or extracellular export (page 42, lines 17-19), and peptide sequence tags to facilitate fusion molecule purification the fusion molecules (page 42, lines 29-31) are also described.

In view of the fusion molecules described above and the level of skill in the art, Applicants assert that sufficient representative fusion molecules are adequately described in the Specification (without undue detail) to support a genus of fusion molecules, as recited in Claim

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1, and all claims dependent on Claim 1. Applicants respectfully request the withdrawal of this rejection.

*Fusion Molecules Comprising First and/or Second Polypeptide Sequences Having "90% Sequence Identity" with an Ig Heavy Chain Constant Region are Adequately Described*

The Examiner alleges that the Specification fails to provide sufficient written description of polypeptides having at least 90% sequence identity with the IgG and IgE constant domain sequences (*e.g.*, 90% sequence identity with SEQ ID NOs: 3 and 6) where the molecules retain biological activity.

Applicants respectfully traverse the rejection. Applicants point out that the Specification describes methods for the determination of percent identity between two amino acid sequences (see Specification, page 14, line 25 through page 15, line 3). Also, the Specification provides examples of prior art that describes numerous Ig Fc polypeptides having at least 90% sequence identity with the Fc sequences of SEQ ID NOs: 3 and 6 (*see*, the Specification at page 17, line 21 through page 18, line 3). The Specification also describes methods for the identification of Ig Fc sequences having at least 90% sequence identity with the constant domain sequences of SEQ ID NOs: 3 and 6 (see the Specification at page 15, lines 4-30). Alternatively still, one of ordinary skill in the art can readily engineer novel Fc domains having at least 90% sequence identity with the constant domain sequences of SEQ ID NOs: 3 and 6 using recombinant DNA/protein engineering techniques.

Applicants point out that all pending claims reciting polypeptides having at least 90% sequence identity with IgG or IgE Fc domains (*e.g.*, having 90% sequence identity with SEQ ID NOs: 3 or 6) contain the functional limitation that the polypeptides also have the ability to bind to their respective cell surface receptors. The Specification provides description of this limitation where the amino acids necessary for receptor binding and biological activity (page 21, lines 9-28) and methods to determine the affinity of an Fc domain for its cognate receptor (see, for example, page 26, lines 15-25) are described.

Applicants argue that the Specification provides adequate written description for fusion molecules comprising polypeptides having at least 90% sequence identity with IgG or IgE constant domain sequences (*e.g.*, 90% sequence identity with SEQ ID NOs: 3 and 6), especially in view of the state of the prior art, and the high level of skill in the art. Applicants further argue

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that the scope of the claims (*i.e.*, Claims 29, 42 and 54, and all claims dependent on those claims) finds written description throughout the Specification, and are allowable. The Examiner is respectfully requested to withdraw this rejection.

*"Hybridizing Under Stringent Conditions" is Adequately Described in the Specification*

The Examiner alleges that the fusion molecules of Claims 40 and 41 are not supported by adequate written description. The Examiner states "the nucleic acid can encompass an infinite number of nucleic acid that are capable of hybridizing under any conditions, including low stringency, to any undisclosed 'nucleic acid molecule'," resulting in "the indefinite number of 'nucleic acid' that may encompassed by the claims 40 and 41" (Office Action, page 8, paragraph starting on line 9).

Applicants disagree with the Examiner's rejection. Contrary to the Examiner's statements, use of stringent hybridization conditions does not result in an infinite number of nucleic acids capable of hybridizing to an IgG or IgE Fc domain under any conditions. Hybridization under stringent conditions yields a limited number of nucleic acids having relatively high degrees of homology with the target sequence. Furthermore, as required by Claim 1, the polypeptides encoded by the sequences which hybridize under stringent conditions must also contain amino acid sequences to permit specific binding to a native IgG or IgE receptor<sup>3</sup>. Applicants argue that sufficient written description has been provided in the Specification for one of skill in the art to recognize that the Applicants have described "*hybridizing under stringent conditions*" with sufficient detail but without undue detail.

Applicants assert that Claims 40 and 41, as originally filed, find sufficient written description in the Specification, and are allowable. However, solely for the purpose of better defining the invention, furthering the Applicants' business interests and advancing the prosecution of the present application, and while reserving the right to prosecute the original or similar claims in the future without loss of equivalents, Applicants have amended Claims 40 and 41 to recite exemplary stringent hybridization conditions, as described *supra*. Applicants respectfully request the withdrawal of this rejection.

(3) *Amended Claims do not Contain New Matter*

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In the Office Action, the Examiner rejects Claims 1-6, 22-27, 29-30, and 40-54 for allegedly containing new subject matter that represents a departure from the originally filed specification and claims (35 U.S.C. § 112, first paragraph), as the originally filed specification and claims do not have support for "other than an antibody variable region" (Office Action, page 8, section 8).

Applicants must respectfully disagree.

First of all, it is noted that claims 53 and 54 were erroneously included in this rejection, since they are independent claims, which do not include the language on which the present rejection is based. In addition, it is clear from the entirety of the specification as originally filed that the present invention concerns fusion molecules, other than bispecific antibodies, in which the two binding regions specified in the claims would not be antibody variable regions. Indeed, the fusion molecules bind two different types of immunoglobulin receptors, which are also referred to as "Fc" receptors, to reflect that they bind the constant region (and not the variable region) of immunoglobulins. (See, e.g. page 1, lines 17-19 of the specification.) The language objected to was added merely to more clearly reflect this fact, and should not be viewed as new matter.

#### Rejections under 35 U.S.C. 112, second paragraph

In the Office Action, the Examiner rejects Claims 40 and 41 for allegedly being indefinite (35 U.S.C. § 112, second paragraph). The Examiner alleges "the recitation of hybridizing 'under stringent conditions' in claims 40-41 is indefinite" (Office Action, page 9, section 10).

Applicants must respectfully disagree. Applicants note that stringency and stringent hybridization are amply described in the Specification (see page 15, lines 4-30). Applicants assert that in view of this disclosure in the Specification, Claims 40 and 41 are definite with regard to "stringent conditions," and those claims are in condition for allowance. However, solely for the purpose of better defining the invention, furthering the Applicants' business interests and advancing the prosecution of the present application, and while reserving the right to prosecute the original or similar claims in the future without loss of equivalents, Applicants have amended Claims 40 and 41 to recite exemplary stringent hybridization conditions. Support

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<sup>3</sup> Amino acids involved in the specific interaction of IgG Fc or IgE Fc domains with a native IgG or IgE receptor are taught on page 21, lines 9-28.

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for this amendment is found in the Specification at page 15, lines 25-30. Applicants respectfully request the withdrawal of the present rejection.

Claim Rejections Under 35 U.S.C. § 103(a)

(1) Claims 1-6, 27, 29-30, 40-43, 47-48 and 73-76 stand rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,336,603 (issued August 9, 1994) in view of Krauss *et al.* (*Eur. J. Immunol.*, 25:192-199 [1995]) and Basu *et al.* (*J. Biol. Chem.*, 268(18):13118-13127 [1993]).

U.S. Patent No. 5,336,603, in its relevant part, describes fusion molecules (immunoadhesins) comprising a soluble receptor (*e.g.*, the CD4 T-cell receptor) fused to immunoglobulin (*e.g.*, IgG) constant domain sequences. It is intended that these soluble CD4-IgG fusion molecules find use in suppressing HIV infectivity by non-productive interaction with HIV via engagement of the HIV gp120 protein. Inclusion of IgG Fc sequences in the fusion protein serve to enhance the half-life of the soluble CD4.

Krauss *et al.* describe fusion molecules containing CD4 receptor sequences and immunoglobulin IgE heavy chain constant domain sequences, and specifically, Cε2, Cε3 and Cε4 sequences. These authors show binding of this fusion molecule to the FcεRI and FcεRII receptors. It is intended by these authors that the fusion molecule will inhibit HIV replication by engaging the HIV gp120 protein on the virus, and simultaneously tethering the HIV to mast cells and basophils that have been *activated* by the IgE Fc component on the fusion protein.

Basu *et al.* describe the isolation of purified portions of the IgE Fc domain. These purified sequences are in the form of fusion molecules, where the IgE sequences are fused to a short portion of the IL-2 receptor that serves as a tag to aid in secretion of the expressed protein.

The Examiner alleges that it is obvious that the CD4 sequences in the fusion molecules of U.S. Patent No. 5,336,603 can be replaced by the IgE Fc sequences of Krauss *et al.* or Basu *et al.* to yield an IgG-IgE Fc fusion molecule of the present invention. Applicants assert that the Examiner has improperly combined references to arrive at the present invention. Applicants can discern no motivation to make such a combination to arrive at a fusion molecule containing both IgG and IgE sequences, either implicit or implied. Applicants point out that a proposed combination of references can not render the prior art unsatisfactory for its intended purpose or change the principle of operation of a reference (MPEP 2143.01 and 2145; also, see especially *In*

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*re Gordon*, 733 F.2d 900, 221 USPQ 1125 [Fed. Cir. 1984] and *In re Ratti*, 270 F.2d 810, 123 USPQ 349 [CCPA 1959]).

As stated above, the prior art described in U.S. Patent No. 5,336,603 and Krauss *et al.* describe fusion molecules for the purpose of suppressing HIV proliferation. Both of these references incorporate CD4 protein sequences as a necessary component of the fusion molecules. Native (*i.e.*, endogenous) CD4 protein is expressed on the surface of various T-cell subpopulations and serves as the HIV entry point during T-cell HIV infection. In the case of U.S. Patent No. 5,336,603, soluble chimeric (*i.e.*, fusion) forms of the CD4 receptor serve as “decoy” or “dummy” molecules to divert HIV from infecting T-cells. In Krauss *et al.*, the CD4 moiety acts as a tether to bring the HIV virion into the proximity of *activated* mast cells, and thereby make the HIV virion prone to immune attack. In both prior art examples, the CD4 sequences are absolutely required for function of the fusion molecules. Replacement of the CD4 sequences with any other type of sequences would render the fusion molecules unsatisfactory for HIV inhibition. Indeed, the mechanism of this prior art is entirely dependent on the presence of CD4 sequences in the fusion proteins. Applicants assert that there is no motivation to replace the CD4 sequences with any other sequences, as neither U.S. Patent No. 5,336,603, Krauss *et al.* nor Basu *et al.* provide any expectation of success or motivation to produce an IgG-IgE fusion molecule.

In view of the argument above, Applicants assert that the combination of U.S. Patent No. 5,336,603, Krauss *et al.* and Basu *et al.* is improper, and respectfully request the withdrawal of this rejection.

(2) Claims 22-26 and 49-53 stand rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,336,603, in view of Krauss *et al.* and Basu *et al.*, and further in view of WO 88/09344 (published 1988). The Examiner alleges that IgG-IgE Fc fusion molecules of the present invention are obvious over U.S. Patent No. 5,336,603 in view of Krauss *et al.* and Basu *et al.*, and furthermore, the fusion molecule may contain a polypeptide linker sequence, as taught in WO 88/09344.

As discussed above, Applicants assert that the combination of U.S. Patent No. 5,336,603, Krauss *et al.* and Basu *et al.* to arrive at the invention is improper. As the present rejection is also dependent on the combination of these three references, Applicants assert that this present rejection is also invalid, and respectfully request withdrawal of the rejection.

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(3) Claim 30 stands rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,336,603, in view of Krauss *et al.* and Basu *et al.*, and further in view of U.S. Patent No. 5,925,351 (issued July 1999). The Examiner alleges that IgG-IgE Fc fusion molecules of the present invention are obvious over U.S. Patent No. 5,336,603 in view of Krauss *et al.* and Basu *et al.*, and furthermore, the fusion molecule may contain a polypeptide having at least 90% amino acid sequence identity with IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub> or IgG<sub>4</sub>, as taught in U.S. Patent No. 5,925,351.

As discussed above, Applicants assert that the combination of U.S. Patent No. 5,336,603, Krauss *et al.* and Basu *et al.* to arrive at the invention is improper. As the present rejection is also dependent on the combination of these three references, Applicants assert that this present rejection is also invalid, and respectfully request withdrawal of the rejection.

(4) Claims 44-46 stand rejected under 35 U.S.C. §103(a) as obvious over U.S. Patent No. 5,336,603, in view of Krauss *et al.* and Basu *et al.*, and further in view of Stevenson *et al.* (*Jour. Immunol.*, 158(5):2242-2250 [1997]). The Examiner alleges that IgG-IgE Fc fusion molecules of the present invention are obvious over U.S. Patent No. 5,336,603 in view of Krauss *et al.* and Basu *et al.*, and furthermore, the fusion molecule may contain a polypeptide having at least part of the hinge of a native human IgG<sub>1</sub> Fc, as taught in Stevenson *et al.*

As discussed above, Applicants assert that the combination of U.S. Patent No. 5,336,603, Krauss *et al.* and Basu *et al.* to arrive at the invention is improper. As the present rejection is also dependent on the combination of these three references, Applicants assert that this present rejection is also invalid, and respectfully request withdrawal of the rejection.

Applicants have reviewed the remaining references that were made of record by the Examiner, but not relied upon in rejecting the Applicant's claims. These references do not teach or suggest Applicant's claimed invention as set forth in the Applicants' application.

#### SUMMARY

For the reasons set forth above, Applicants believe that all claims pending in this application are in condition for allowance. Should the Examiner believe that a telephone interview would expedite the prosecution of this Application, Applicants invite the Examiner to call the undersigned attorney at the telephone number indicated below.

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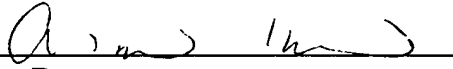
Please charge any additional fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 11-1410. A duplicate copy of this sheet is enclosed.

Attached hereto at the APPENDIX is a marked-up version of claims and portions of the specification indicating the changes made to these sections by the current amendment. For the Examiner's convenience, all pending claims in the application are shown, where claims not changed by the present amendment are shown in italics. The attached APPENDIX is captioned **"Version with markings to show changes made."**

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: January 8, 2002

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## APPENDIX I

Revision with markings to show changes made

Deleted text is shown with strikethrough and added text is shown with underlining.

### IN THE SPECIFICATION:

The paragraph consisting of lines 12 through 19 on page 2 has been amended as follows:

--Through the high-affinity IgE receptor, FcεRI, IgE plays key roles in an array of acute and chronic allergic reactions, including asthma, allergic rhinitis, atopic dermatitis, severe food allergies, chronic urticaria and angioedema, as well as the serious physiological condition of anaphylactic shock as results, for example, from bee stings or penicillin allergy. Binding of a multivalent antigen (allergen) to antigen-specific IgE specifically bound to FcεRI on the surface of mast cells and basophils stimulates a complex series of signaling events that culminate in the release of host vasoactive and proinflammatory mediators contributing to both acute and late-phase allergic responses (Metcalf *et al.*, *Physiol. Rev.* 77:1033-1079 (1997)).--

The paragraph spanning page 2 (line 28) through page 3 (line 9) has been amended as follows:

--Along with the stimulatory FcεRI, mast cells and basophils co-express an immunoreceptor tyrosine-based inhibition motif (ITIM)-containing inhibitory low-affinity receptor, FcγRIIb, that acts as a negative regulator of antibody function. FcγRIIb represents a growing family of structurally and functionally similar inhibitory receptors, the inhibitory receptor superfamily (IRS), that negatively regulate ITAM-containing immune receptors (Ott and Cambier, *J. Allergy Clin. Immunol.*, 106:429-440 (2000)) and a diverse array of cellular responses. Coaggregation of an IRS member with an activating receptor leads to phosphorylation of the characteristic ITIM tyrosine and subsequent recruitment of the SH2 domain-containing protein tyrosine ~~phosphatases~~ phosphatases, SHP-1 and SHP-2, and the SH2 domain-containing phospholipases, SHIP and SHIP2 (Cambier, J.C., *Proc. Natl. Acad. Sci. USA*, 94:5993-5995 (1997)). Possible outcomes of the coaggregation include inhibition of cellular activation, as demonstrated by the coaggregation of FcγRIIb and B-cell receptors, T-cell receptors, activating receptors, including FcεRI, or cytokine receptors (Malbec *et al.*, *Curr. Top. Microbiol. Immunol.*, 244:13-27 (1999)).--

The paragraph consisting of lines 10 through 24 on page 3 has been amended as follows:

--Most studies have so far concentrated on elucidating the mechanisms of FcγRII, in particular FcγRIIb, function. The three alternatively spliced isoforms of the FcγRIIb receptor, of which FcγRIIb1' is only found in mice, and FcγRIIb1 and FcγRIIb2 are expressed in both humans and mice, have Ig-like loops and a conserved ITIM, but differ in their cytoplasmic domains. Co-crosslinking of the high-affinity FcεRI receptor and the inhibitory low-affinity receptor FcγRII blocks a number of processes, including FcεRI-mediated secretion, IL-4 production, Ca<sup>2+</sup> mobilization, Syk phosphorylation, and FcεRI-mediated basophil and mast cell activation. In B cells, co-crosslinking of the B-cell receptor and FcγRIIb inhibits B-cell receptor-mediated cell activation (Cambier, J.C., *Proc. Natl. Acad. Sci.*, 94:5993-5995 (1997); Daeron, M., *Annu. Rev. Immunol.*, 5 15:203-234 (1997)), and specifically, inhibits B-cell receptor-induced blastogenesis and proliferation (Chan et al., *Immunology*, 21:967-981 (1971); Phillips and Parker, *J. Immunol.*, 132:627-632 (1984)) and stimulates apoptosis (Ashman et al., *J. Immunol.*, 157:5-11 (1996)). Coaggregation of FcγRIIb1 or FcγRIIb2 with FcεRI in rat basophilic leukemia cells, inhibits FcεRI-mediated release of serotonin and TNF-α (Daeron et al., *J. Clin. Invest.*, 95:577-85 (1995); Daeron et al., *Immunity*, 3:635-646 (1995)).--

The paragraph consisting of lines 3 through 9 on page 10 has been amended as follows:

--The binding is "specific" when the binding affinity of a molecule for a binding target, e.g. an IgG or IgE receptor, is significantly higher (preferably at least about 2-times, more preferably at least about 4-times, most preferably at least about 6-times higher) than the binding affinity of that molecule to any other known native polypeptide.~~Since you do not define how one determines the universe of "other known native polypeptide(s)", this definition could be considered indefinite. What about defining specific binding as preferential binding in the presence of a competitor (you could even name possible competitors).--~~

The paragraph consisting of lines 13 through 27 on page 10 has been amended as follows:

--The terms "receptor comprising an immune receptor tyrosine-based inhibitory motif (ITIM)" and "ITIM-containing receptor" is are used to refer to a receptor containing one or more immune receptor tyrosine-based inhibitory motifs, ITIMs. The ITIM motif can be generally

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represented by the formula Val/Ile-Xaa-PTyr-Xaa-Xaa-Leu/Val (where Xaa represents any amino acid). ITIM-containing receptors include, without limitation, FcγRIIb, gp49b1/gp91 (Arm *et al.*, *J. Biol. Chem.* 266:15966-73 (1991)), p91/PIR-B (Hayami *et al.*, *J. Biol. Chem.* 272:7320-7 (1997)), LIR1-3, 5, 8, LAIR-1; CD22 (van Rossenberg *et al.*, *J. Biol. Chem.* January 4, 276(16):12967-12973 [2001]); CTL-4, CD5, p58/70/140 KIR, PIRB2-5; NKB1, Ly49 A/C/E/F/G, NKG2-A/B, APC-R, CD66, CD72, PD-1, SHPS-1, SIRP-α1, IL T1-5, MIR7, 10, hMIR(HM18), hMIR(HM9), Fas(CD95), TGFβ-R, TNF-R1, IFN-γ-R (α- and β-chains), mast cell function Ag, H2-M, HLA-DM, CD1, CD1-d, CD46, c-cbl, Pyk2/FADK2, P130 Ca rel prot, PGDF-R, LIF, LIR-R, CIS, SOCS13 and 3, as reviewed in Sinclair NR *et al.*, *supra*. Ligands for many of these receptors are also known, such as, e.g. the ligand for CD95 is called CD95 ligand, the ligands for CTLA-4 are CD80 and CD86, the ligands of IFN-γ receptor is IFN-γ, etc. Ligands for CD22 comprise the basic binding motif Nau5Ac-a(2,6)-Lac, and are discussed, for example in van Rossenberg *et al.*, 2001, *supra*.--

The paragraph consisting of lines 6 through 14 on page 23 has been amended as follows:

--The second polypeptide sequence present in the fusion molecules of the invention preferably has at least about 80%, more preferably at least about 85%, even more preferably at least about 90%, yet more preferably at least about 95%, most preferably at least about 99% sequence identity with the amino acid sequence of the CH2-CH3-CH4 region of a native IgE immunoglobulin, preferably native human IgE, or with the sequence of a native allergen protein. In a particularly preferred embodiment, the sequence identity is defined with reference to the human CHε2-CHε3-CHε4 sequence of SEQ ID NO: 6 or with regard to one of the allergen sequences listed in Table 1 below (SEQ ID NOS: 7 ~~8~~ through 173), or, in a preferred embodiment, ~~one of two Ara h2 clones represented by SEQ ID NOS: 174 and 175, respectively a peanut allergen, e.g., Ara h1, Ara h2 or Ara h3 (see, SEQ ID NOS: 27-28 and 176-177).~~--

TABLE 1, on page 30 (see SEQ ID NO: 12) has been amended as follows:

Alt a 12	RLA1_ALTAL	P49148	60S Acidid <u>Acidic</u> <del>Ribosomal</del> <u>Ribosomal</u> Protein P1	Alternaria alternata	12
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TABLE 1, on page 38 (see row between SEQ ID NOs: 141 and 143) has been amended as follows:

Phl p 6	MPP6_PHLPR	P43215	Pollen Allergen Phl p 6 [Precursor]	Phleum pratense (Common timothy)	<del>141</del> <u>142</u>
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The paragraph consisting of lines 12 through 25 on page 41 has been amended as follows:

--Host cells can be any eukaryotic or prokaryotic hosts known for expression of heterologous proteins. Accordingly, the polypeptides of the present invention can be expressed in eukaryotic hosts, such as eukaryotic microbes (yeast) or cells isolated from multicellular organisms (mammalian cell cultures), plants and insect cells. Examples of mammalian cell lines suitable for the expression of heterologous polypeptides include monkey kidney CV1 cell line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney cell line 293S (Graham *et al*, *J. Gen. Virol.* 36:59 [1977]); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary (CHO) cells (Urlaub and Chasin, *Proc. Natl. Acad. Sci. USA* 77:4216 [1980]; monkey kidney cells (CVI-76, ATCC CCL 70); African green monkey cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); human lung cells (W138, ATCC CCL 75); and human liver cells (Hep G2, HB 8065). In general myeloma cells, in particular those not producing any endogenous antibody, e.g. the non-immunoglobulin producing ~~myelome~~ myeloma cell line SP2/0, are preferred for the production of the fusion molecules herein.

The paragraph consisting of lines 10 through 23 on page 43 has been amended as follows:

--In certain instances, especially if the two polypeptide sequences making up the bifunctional molecule of the present invention are connected with a non-polypeptide linker, it may be advantageous ~~the~~ to individually synthesize the first and second polypeptide sequences, e.g. by any of the recombinant approaches discussed above, followed by functionally linking the two sequences.--

The paragraph spanning page 43 (line 24) through page 44 (line 10) has been amended as follows:

--The fusion molecules of the present invention may include amino acid sequence variants of native immunoglobulin (e.g. IgG and/or IgE) or allergen (e.g., Ara h 2 sequences).

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Such amino acid sequence variants can be produced by expressing the underlying DNA sequence in a suitable recombinant host cell, or by *in vitro* synthesis of the desired polypeptide, as discussed above. The nucleic acid sequence encoding a polypeptide variant is preferably prepared by site-directed mutagenesis of the nucleic acid sequence encoding the corresponding native (e.g. human) polypeptide. Particularly preferred is site-directed mutagenesis using polymerase chain reaction (PCR) amplification (see, for example, U.S. Pat. No. 4,683,195 issued 28 July 1987; and Current Protocols In Molecular Biology, Chapter 15 (Ausubel *et al.*, ed., 1991). Other site-directed mutagenesis techniques are also well known in the art and are described, for example, in the following publications: Current Protocols In Molecular Biology, *supra*, Chapter 8; Molecular Cloning: A Laboratory Manual, 2<sup>nd</sup> edition (Sambrook *et al.*, 1989); Zoller *et al.*, Methods Enzymol. 100:468-500 (1983); Zoller & Smith, DNA 3:479-488 (1984); Zoller *et al.*, Nucl. Acids Res., 10:6487 (1987); Brake *et al.*, Proc. Natl. Acad. Sci. USA 81:4642-4646 (1984); Botstein *et al.*, Science 229:1193 (1985); Kunkel *et al.*, Methods Enzymol. 154:367-82 (1987), Adelman *et al.*, DNA 2:183 (1983); and Carter *et al.*, Nucl. Acids Res., 13:4331 (1986). Cassette mutagenesis (Wells *et al.*, Gene, 34:315 [1985]), and restriction selection mutagenesis (Wells *et al.*, Philos. Trans. R. Soc. London SerA, 317:415 [1986]) may also be used.--

The paragraph consisting of lines 6 through 12 on page 46 has been amended as follows:

--*Uses of compounds for targeted diseases* The compounds disclosed herein can be used to inhibit acute or ~~chronically~~ chronic ~~inhibit~~ IgE mediated ~~reaction~~ reactions to major environmental and occupational allergens, can be used to provide for allergy vaccination (immunotherapy) to induce a state of non-allergic reactivity to specific allergens and can also have a prophylactic effect against allergic disease by preventing allergic sensitization to environmental and occupational allergens when administered to at-risk individuals (e.g., those at genetic risk of asthma and those exposed to occupational allergens in the workplace).--

The paragraph spanning page 46 (line 23) through page 47 (line 8) has been amended as follows:

--The present invention as of gamma allergen bifunctional fusion molecules provides for a novel form of allergy vaccination that will be safer and more effective in the treatment of a

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~~varieties~~ variety of IgE mediated allergic reactivity, including, without limitation, asthma, allergic rhinitis, atopic dermatitis, food allergies, urticaria and angioedema, up to and including anaphylactic shock. Having the allergen fused to a molecule that will bind to FcγRIIb on mast cells and basophils will prevent the allergen being able to induce local or systemic allergic reactions. Such local or systemic allergic reactions are major problem in allergen vaccination as currently practiced. The gamma-allergen fusion proteins will be able to be given in higher doses over a shorter interval and with greater safety than standard allergen therapy. In addition, use of the gamma-allergen compounds will cause antigen specific desensitization to that specific allergen. Thus the gamma-allergen compounds will give a window of safe exposure to the allergen be it as an acute or recurring treatment as would be needed in using a therapeutic monoclonal antibody to which a patient has developed an allergic (IgE) response or as chronic treatment for prevention of unintentional exposures such as occurs with peanut allergens. This use is expected to gain added importance, as the number of recombinant biological products entering the clinical arena will be increasing dramatically in the near future. The gamma-allergen compounds can even be used along with conventional allergen vaccination so as to provide an extra margin of safety while large doses of standard allergen are given.--

The paragraph consisting of lines 9 through 28 on page 47 has been amended as follows:

--In addition, the chimeric gamma-epsilon compounds herein hold great promise for the treatment of chronic urticaria and angioedema. Urticaria is a skin symptom that may accompany allergies but often is idiopathic. It is a relatively common disorder caused by localized cutaneous mast cell degranulation, with resultant increased dermal vascular permeability culminating in pruritic wheals. Angioedema is a vascular reaction involving the deep dermis or subcutaneous or submucosal tissues caused by localized mast cell degranulation. This results in tissue swelling that is pruritic or painful. Chronic urticaria and angioedema often occur together although they occur individually as well. These conditions are common and once present for more than six months, they often last a decade or more. Although not fatal, they are very troubling to patients, as the frequent recurring ~~attaching~~ attacks disrupt daily activities and thereby result in significant morbidity. Standard therapy is often unsuccessful in treating these conditions, ~~and they which~~ are distressing to the point that chemotherapy with cyclosporine and other potent immunosuppressive drugs has recently been advocated. Increasing evidence suggests that as

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many as 60% of patients with these conditions actually have an autoimmune disease, in which they make functional antibodies against the FcεRI receptor. For further details, see Hide *et al.*, *N. Engl. J. Med.* 328:1599-1604 (1993); Fiebiger *et al.*, *J. Clin. Invest.* 96:2606-12 (1995); Fiebiger *et al.*, *J. Clin. Invest.* 101:243-51 (1998); Kaplan, A.P., *Urticaria and Angioedema, In: Inflammation: Basic Principles and Clinical Correlates* (Gallin and Snyderman eds.), 3<sup>rd</sup> Edition, Lippincott & Wilkins, Philadelphia, 1999, pp. 915-928. The fusion molecules of the present invention are believed to form the basis for a novel and effective treatment of these diseases by safely blocking access to the FcεRI.--

The paragraph spanning page 52 (line 27) through page 53 (line 2) has been amended as follows:

--*Expression and Purification* - The expression vector containing chimeric Fcγ-Fcε gene was linearized at the ~~PeuI~~ PvuI site and transfected into SP2/0 cells by electroporation (Bio-Rad). Stable transfectants were selected for growth in medium containing 1 mg/ml geneticine. Clones producing the fusion protein were identified by ELISA using plates coating anti-human IgE (CIA7.12) or IgG (Sigma) antibody. Supernatants from clones were added to wells, and bound protein was detected using goat anti-human IgE or IgG conjugated to alkaline phosphatase (KPL). The fusion protein was purified from the supernatants and ascites by using rProtein A column (Pharmacia).--

The paragraph consisting of lines 3 through 7 on page 53 has been amended as follows:

--*Western Blotting* - The purified protein was run on 7.5% SDS polyacrylamide gel. After transfer, the nylon membrane was blocked by 4% bovine serum albumin/PBS/Tween overnight at 4 °C. For protein detection, the blot was probed with either goat anti-human IgE (ε chain specific) or goat anti-human IgG (γ chain-specific) conjugated to alkaline ~~psephatase~~ phosphatase (KPL). Color development was performed with an alkaline phosphatase conjugated substrate kit (Bio-Rad).--

#### IN THE CLAIMS:

Claims 40 and 41 have been amended as follows. In the following section the unamended claims are shown in italics for the Examiner's convenience.

1. (Once Amended) An isolated fusion molecule comprising a first polypeptide sequence, other than an antibody variable region, capable of specific binding to a native IgG inhibitory receptor comprising an immune receptor tyrosine-based inhibitory motif (ITIM), expressed on mast cells, basophils or B cells, functionally connected to a second polypeptide sequence, other than an antibody variable region, capable of specific binding directly to a native IgE receptor (FcεR).

2. The fusion molecule of claim 1 wherein said inhibitory receptor is a low-affinity IgG receptor FcγRIIb.

3. The fusion molecule of claim 2 wherein said IgE receptor is a high-affinity FcεRI receptor.

4. The fusion molecule of claim 2 wherein said IgE receptor is a low-affinity IgE receptor FcεRII (CD23).

5. The fusion molecule of claim 3 wherein said FcγRIIb and FcεRI receptors are of human origin.

6. The fusion molecule of claim 4 wherein said FcγRIIb and FcεRII receptors are of human origin.

22. (Once Amended) The fusion molecule of claim 1 wherein said first and second polypeptide sequences are connected through a linker.

23. The fusion molecule of claim 22 wherein said linker is a polypeptide sequence.

24. The fusion molecule of claim 23 wherein said polypeptide sequence consists of 5 to 25 amino acid residues.

25. The fusion molecule of claim 23 wherein said polypeptide sequence consists of 10 to 25 amino acid residues.

26. The fusion molecule of claim 23 wherein said polypeptide sequence consists of 15 to 25 amino acid residues.

27. The fusion molecule of claim 1 wherein said first and second polypeptide sequences are directly fused to each other.

29. The fusion molecule of claim 3 wherein said first polypeptide comprises an amino acid sequence having at least 90% sequence identity with the hinge-CH2-CH3 portion of an IgG immunoglobulin heavy chain constant region.



30. *The fusion molecule of claim 29 wherein said immunoglobulin is selected from the group consisting of IgG<sub>1</sub>, IgG<sub>2</sub>, IgG<sub>3</sub> and IgG<sub>4</sub>.*

40. (Once Amended) The fusion molecule of claim 3 wherein said first polypeptide sequence comprises a sequence encoded by nucleic acid hybridizing under stringent conditions to the complement of the hinge-CH2-CH3 coding sequence of SEQ ID NO: 1, wherein said first polypeptide sequence is capable of specific binding to a native human FcγRIIb receptor, and wherein said stringent conditions comprise hybridization in 50% formamide, 6X SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5X Denhardt's solution, sonicated salmon sperm DNA (100 μg/ml), 0.5% SDS, and 10% dextran sulfate at 42 °C, with washes at 42 °C in 2X SSC and 0.1% SDS at 55 °C, followed by a high-stringency wash comprising 0.2X SSC comprising 0.1% SDS at 42 °C.

41. (Once Amended) The fusion molecule of claim 3 wherein said second polypeptide sequence comprises a sequence encoded by nucleic acid hybridizing under stringent conditions to the complement of the CH2-CH3-CH4 coding sequence of SEQ ID NO: 4, wherein said second polypeptide sequence is capable of specific binding to a native human FcεRI receptor, and wherein said stringent conditions comprise hybridization in 50% formamide, 6X SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5X Denhardt's solution, sonicated salmon sperm DNA (100 μg/ml), 0.5% SDS, and 10% dextran sulfate at 42 °C, with washes at 42 °C in 2X SSC and 0.1% SDS at 55 °C, followed by a high-stringency wash comprising 0.2X SSC comprising 0.1% SDS at 42 °C.

42. (Once Amended) *The fusion molecule of claim 1 comprising a first polypeptide sequence having at least 90% sequence identity with the amino acid sequence of SEQ ID NO: 3 and capable of specific binding to a native human FcγRIIb receptor, functionally connected to a second polypeptide sequence having at least 90% sequence identity with the amino acid sequence of SEQ ID NO: 6 and capable of specific binding directly to a native human FcεRI receptor.*

43. *The fusion molecule of claim 42 wherein said first polypeptide sequence comprises at least part of the CH2 and CH3 domains of a native human IgG<sub>1</sub> constant region.*

44. *The fusion molecule of claim 43 wherein said first polypeptide sequence additionally comprises at least part of the hinge of a native human IgG<sub>1</sub> constant region.*

45. *The fusion molecule of claim 44 wherein said first polypeptide sequence comprises at least part of the hinge, CH2 and CH3 domains of a native human IgG<sub>1</sub> heavy chain constant region, in the absence of a functional CH1 region.*

46. *The fusion molecule of claim 45 wherein said first polypeptide sequence consists of the hinge, CH2 and CH3 domains of a native human IgG<sub>1</sub> heavy chain constant region.*

47. *The fusion molecule of claim 42 wherein said second polypeptide sequence comprises at least part of the CH2, CH3, and CH4 domains of a native human IgE heavy chain constant region.*

48. *The fusion molecule of claim 47 wherein said second polypeptide sequence consists of the CH2, CH3 and CH4 domains of a native human IgE heavy chain constant region.*

49. *The fusion molecule of claim 48 wherein said second polypeptide sequence is functionally connected to a first polypeptide sequence consisting of the hinge, CH2 and CH3 domains of a native human IgG<sub>1</sub> heavy chain constant region sequence through a polypeptide linker.*

50. *The fusion molecule of claim 49 wherein said polypeptide linker consists of 5 to 25 amino acid residues.*

51. *The fusion molecule of claim 50 wherein said polypeptide linker consists of 10 to 25 amino acid residues.*

52. *The fusion molecule of claim 51 wherein said polypeptide linker consists of 15 to 25 amino acid residues.*

53. *The fusion molecule of SEQ ID NO: 7.*

54. *A fusion molecule having at least 90% sequence identity with SEQ ID NO: 7.*

73. *The fusion molecule of claim 1 covalently linked to a second identical fusion molecule to form a homodimer.*

74. *The fusion molecule of claim 73 wherein said linkage is through one or more disulfide bonds.*

75. *The fusion molecule of claim 42 covalently linked to a second identical fusion molecule to form a homodimer.*

76. *The fusion molecule of claim 75 wherein said linkage is through one or more disulfide bonds.*